

## Claims

1. Epothilone derivatives of general formula I,



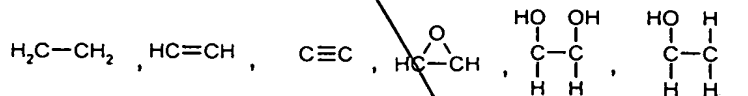
in which

~~R<sup>1a</sup>, R<sup>1b</sup> are the same or different and mean hydrogen, C<sub>1</sub>-C<sub>10</sub> alkyl, aryl, C<sub>7</sub>-C<sub>20</sub> aralkyl, or together a -(CH<sub>2</sub>)<sub>m</sub> group with m = 2, 3, 4 or 5,~~

~~R<sup>2a</sup>, R<sup>2b</sup> are the same or different and mean hydrogen, C<sub>1</sub>-C<sub>10</sub> alkyl, aryl, C<sub>7</sub>-C<sub>20</sub> aralkyl or together a -(CH<sub>2</sub>)<sub>n</sub> group with n = 2, 3, 4 or 5, whereby, if -D-E- stands for -CH<sub>2</sub>-CH<sub>2</sub>- or Y stands for an oxygen atom, R<sup>2a</sup>/R<sup>2b</sup> cannot be hydrogen/methyl,~~

R<sup>3</sup> means hydrogen, C<sub>1</sub>-C<sub>10</sub> alkyl, aryl, C<sub>7</sub>-C<sub>20</sub> aralkyl,

~~R<sup>4a</sup>, R<sup>4b</sup> are the same or different and mean hydrogen, C<sub>1</sub>-C<sub>10</sub> alkyl, aryl, C<sub>7</sub>-C<sub>20</sub> aralkyl or together a -(CH<sub>2</sub>)<sub>p</sub> group with p = 2, 3, 4 or 5,~~



D-E means a group

R<sup>5</sup> means hydrogen, C<sub>1</sub>-C<sub>10</sub> alkyl, aryl, ~~C<sub>7</sub>-C<sub>20</sub> aralkyl,~~

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3. Epothilone derivatives of general formula I according to claim 1, in which  $R^3$ ,  $R^{4a}$ ,  $R^{4b}$ , D-E,  $R^5$ ,  $R^6$  and  $R^7$  all can have the meanings that are indicated in general formula I, and the

remainder of the molecule is identical to naturally occurring epothilone A or B.

4. Epothilone derivatives of general formula I according to claim 1, in which  $R^6$ ,  $R^7$ ,  $R^8$  and X all can have the meanings that are indicated in general formula I, and the remainder of the molecule is identical to naturally occurring epothilone A or B.

5. Epothilone derivatives of general formula I according to claim 1, in which Y, Z,  $R^{1a}$ ,  $R^{1b}$ ,  $R^{2a}$ ,  $R^{2b}$ ,  $R^3$ ,  $R^{4a}$ ,  $R^{4b}$ , D-E,  $R^5$ ,  $R^6$  and  $R^7$  all can have the meanings that are indicated in general formula I, and the remainder of the molecule is identical to naturally occurring epothilone A or B.

6. Epothilone derivatives of general formula I according to claim 1, in which Y, Z,  $R^{1a}$ ,  $R^{1b}$ ,  $R^{2a}$ ,  $R^{2b}$ ,  $R^6$ ,  $R^7$ ,  $R^8$  and X all can have the meanings that are indicated in general formula I, and the remainder of the molecule is identical to naturally occurring epothilone A or B.

7. Epothilone derivatives of general formula I according to claim 1, in which  $R^3$ ,  $R^{4a}$ ,  $R^{4b}$ , D-E,  $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$  and X all can have the meanings that are indicated in general formula I, and the remainder of the molecule is identical to naturally occurring epothilone A or B.

8. Compounds of general formula I, namely

(4S,7R,8S,9S,13(Z),16S(E))-4,8-Dihydroxy-7-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione, and

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(4S,7R,8S,9S,13E,16S(E))-4,8-dihydroxy-7-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione (B)

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione and

(1R,3S(E),7S,10R,11S,12S,16S)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(1S,3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione and

(1R,3S(E),7S,10R,11S,12S,16R)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7S,8R,9S,13Z,16S(E))-4,8-Dihydroxy-7-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione and

(4S,7S,8R,9S,13E,16S(E))-4,8-dihydroxy-7-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10S,11R,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-

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4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione, and

(1R,3S(E),7S,10S,11R,12S,16S)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(1S,3S(E),7S,10S,11R,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione, and

(1R,3S(E),7S,10S,11R,12S,16S)-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-ethyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13(Z),16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-((3-pyridyl)ethenyl)-1-oxa-cyclohexadec-13-ene-2,6-dione, and

(4S,7R,8S,9S,13E,16S(E))-4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-((3-pyridyl)ethenyl)-1-oxa-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-((3-pyridyl)ethenyl)-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione, and

(1S,3S(E),7S,10R,11S,12S,16S)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-((3-pyridyl)ethenyl)-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

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(4S,7R,8S,9S,13(Z),16S(E))-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-((4-pyridyl)ethenyl)-1-oxa-cyclohexadec-13-ene-2,6-dione, and

(4S,7R,8S,9S,13E,16S(E))-4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-((4-pyridyl)ethenyl)-1-oxa-cyclohexadec-13-ene-2,6-dione

(1S,3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-((4-pyridyl)ethenyl)-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione, and

(1S,3S(E),7S,10R,11S,12S,16S)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-((4-pyridyl)ethenyl)-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-7-phenyl-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-phenyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(1(R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-10-phenyl-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

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(4S,7R,8S,9S,13(E or Z),16S(E))-7-Benzyl-4,8-dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethyl-cyclohexadec-13-ene-2,6-dione

(1(S or R),3S(E),7S,10R,11S,12S,16R)-10-Benzyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(1(R or S),3S(E),7S,10R,11S,12S,16S)-10-Benzyl-7,11-dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-tetramethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,13-tetramethyl-9-trifluoromethyl-cyclohexadec-13-ene-2,6-dione

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,16-tetramethyl-12-trifluoromethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

(1(R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,16-tetramethyl-12-trifluoromethyl-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione

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(4S,7R,8S,9S,11E/Z,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-11,13-diene-2,6-dione

(1(S or R),3S(E),7S,10R,11S,12S,14E/Z,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadec-14-ene-5,9-dione

(1(R or S),3S(E),7S,10R,11S,12S,14E/Z,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadec-14-ene-5,9-dione

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,9,13-pentamethyl-cyclohexadec-13-ene-11-ene-2,6-dione

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadec-14-ene-5,9-dione

(1(R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadec-14-ene-5,9-dione

(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,7,9-tetramethyl-13-trifluoromethyl-cyclohexadec-13-ene-2,6-dione

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(1(S or R), 3S(E), 7S, 10R, 11S, 12S, 16R)-7, 11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8, 8, 10, 12-tetramethyl-16-trifluoromethyl-4, 17-dioxabicyclo[14.1.0]heptadeca-5, 9-dione

(1(R or S), 3S(E), 7S, 10R, 11S, 12S, 16S)-7, 11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8, 8, 10, 12-tetramethyl-16-trifluoromethyl-4, 17-dioxabicyclo[14.1.0]heptadeca-5, 9-dione

(4S, 7R, 8S, 9S, 13(E or Z), 16S(E))-4, 8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-13-pentafluoroethyl-5, 5, 7, 9-tetramethyl-cyclohexadec-13-ene-2, 6-dione

(1(S or R), 3S(E), 7S, 10R, 11S, 12S, 16R)-7, 11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-16-pentafluoroethyl-8, 8, 10, 12-tetramethyl-4, 17-dioxabicyclo[14.1.0]heptadeca-5, 9-dione

(1(R or S), 3S(E), 7S, 10R, 11S, 12S, 16S)-7, 11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-16-pentafluoroethyl-8, 8, 10, 12-tetramethyl-4, 17-dioxabicyclo[14.1.0]heptadeca-5, 9-dione

(4S, 7R, 8S, 9S, 13(E or Z), 16S(E))-4, 8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5, 5-(1, 3-trimethylene)-7, 9, 13-trimethyl-cyclohexadec-13-ene-2, 6-dione

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(1(S or R), 3S(E), 7S, 10R, 11S, 12S, 16R)-7, 11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8, 8-(1, 3-trimethylene)-10, 12, 16-trimethyl-4, 17-dioxabicyclo[14.1.0]heptadeca-5, 9-dione

(1(R or S), 3S(E), 7S, 10R, 11S, 12S, 16S)-7, 11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8, 8-(1, 3-trimethylene)-10, 12, 16-trimethyl-4, 17-dioxabicyclo[14.1.0]heptadeca-5, 9-dione

(4S, 7R, 8S, 9S, 11E/Z, 13(E or Z), 16S(E))-4, 8-Dihydroxy-13-ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5, 5, 7, 9-tetramethyl-cyclohexadec-11, 13-diene-2, 6-dione

(1(S or R), 3S(E), 7S, 10R, 11S, 12S, 14E/Z, 16R)-7, 11-Dihydroxy-16-ethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8, 8, 10, 12-tetramethyl-4, 17-dioxabicyclo[14.1.0]heptadec-14-ene-5, 9-dione

(1(R or S), 3S(E), 7S, 10R, 11S, 12S, 14E/Z, 16S)-7, 11-Dihydroxy-16-ethyl-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8, 8, 10, 12-tetramethyl-4, 17-dioxabicyclo[14.1.0]heptadec-14-ene-5, 9-dione

(4S, 7R, 8S, 9S, 11E/Z, 13(E or Z), 16S(E))-4, 8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-13-propyl-5, 5, 7, 9-tetramethyl-cyclohexadec-11, 13-diene-2, 6-dione

(1(S or R), 3S(E), 7S, 10R, 11S, 12S, 14E/Z, 16R)-7, 11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-16-propyl-8, 8, 10, 12-tetramethyl-4, 17-dioxabicyclo[14.1.0]heptadec-14-ene-5, 9-dione

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(1(R or S), 3S(E), 7S, 10R, 11S, 12S, 14E/Z, 16S)-7, 11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-16-propyl-8, 8, 10, 12-tetramethyl-4, 17-dioxabicyclo[14.1.0]heptadec-14-ene-5, 9-dione

(4S, 7R, 8S, 9S, 13(E or Z), 16S(E))-4, 8-Dihydroxy-16-(1-methyl-2-(2-pyridyl)ethenyl)-1-oxa-5, 5, 7, 9, 13-pentamethyl-cyclohexadec-13-ene-2, 6-dione

(1(S or R), 3S(E), 7S, 10R, 11S, 12S, 16R)-7, 11-Dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-8, 8, 10, 12, 16-pentamethyl-4, 17-dioxabicyclo[14.1.0]heptadecane-5, 9-dione

(1(R or S), 3S(E), 7S, 10R, 11S, 12S, 16S)-7, 11-Dihydroxy-3-(1-methyl-2-(2-pyridyl)ethenyl)-8, 8, 10, 12, 16-pentamethyl-4, 17-dioxabicyclo[14.1.0]heptadecane-5, 9-dione

(4S, 7R, 8S, 9S, 13(E or Z), 16S(E))-4, 8-Dihydroxy-16-(1-methyl-2-(4-pyridyl)ethenyl)-1-oxa-5, 5, 7, 9, 13-pentamethyl-cyclohexadec-13-ene-2, 6-dione

(1(S or R), 3S(E), 7S, 10R, 11S, 12S, 16R)-7, 11-Dihydroxy-3-(1-methyl-2-(4-pyridyl)ethenyl)-8, 8, 10, 12, 16-pentamethyl-4, 17-dioxabicyclo[14.1.0]heptadecane-5, 9-dione

(1(R or S), 3S(E), 7S, 10R, 11S, 12S, 16S)-7, 11-Dihydroxy-3-(1-methyl-2-(4-pyridyl)ethenyl)-8, 8, 10, 12, 16-pentamethyl-4, 17-dioxabicyclo[14.1.0]heptadecane-5, 9-dione

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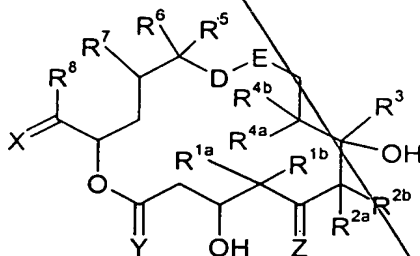
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(4S,7R,8S,9S,13(E or Z),16S(E))-4,8-Dihydroxy-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-5,5,7,9,13-pentamethyl-cyclohexadec-13-en-6-one

(1(S or R),3S(E),7S,10R,11S,12S,16R)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadec-9-one

(1(R or S),3S(E),7S,10R,11S,12S,16S)-7,11-Dihydroxy-3-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-8,8,10,12,16-pentamethyl-4,17-dioxabicyclo[14.1.0]heptadec-9-one.

9. Process for the production of epothilone derivatives of general formula I according to claim 1



I,

in which

the substituents have the meanings that are indicated in general formula I, characterized in that

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## References

Year	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099
1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	

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## References

```

# read in the data
data = read.csv("data.csv")

# create a new variable
data$age_group = ifelse(data$age < 18, "Child",
                        ifelse(data$age < 30, "Young Adult",
                              ifelse(data$age < 50, "Middle-aged",
                                    ifelse(data$age < 65, "Older Adult",
                                            "Senior"))))

# save the data
write.csv(data, "data_with_age_group.csv")

```

including all stereoisomers as well as their mixtures, and free hydroxyl groups in  $R^{13}$  and  $R^{14}$  can be etherified or esterified, free carbonyl groups can be ketalized in A and  $R^{13}$ , converted into an enol ether or reduced, and free acid groups in A can be converted into their salts with bases, is reacted with a fragment of general formula B



in which

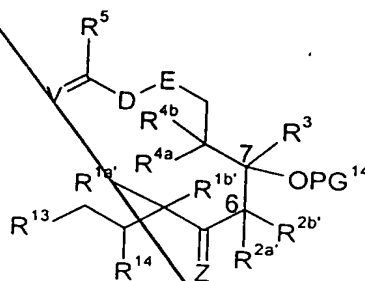
$R^{3'}$ ,  $R^{4a'}$ ,  $R^{4b'}$  and  $R^{5'}$  have the meanings already mentioned for  $R^3$ ,  $R^{4a}$ ,  $R^{4b}$  and  $R^5$ , and

V means an oxygen atom, two alkoxy groups  $OR^{17}$ , a  $C_2-C_{10}$  alkylene- $\alpha,\omega$ -dioxy group, which can be straight-chain or branched or  $H/OR^{16}$ ,

W means an oxygen atom, two alkoxy groups  $OR^{19}$ , a  $C_2-C_{10}$  alkylene- $\alpha,\omega$ -dioxy group, which can be straight-chain or branched or  $H/OR^{18}$ ,

$R^{16}$ ,  $R^{18}$ , independently of one another, mean hydrogen or a protective group  $PG^1$

$R^{17}$ ,  $R^{19}$ , independently of one another, mean  $C_1-C_{20}$  alkyl, to a partial fragment of general formula AB

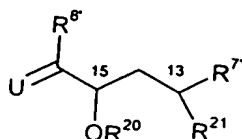


AB,

in which  $R^{1a'}$ ,  $R^{1b'}$ ,  $R^{2a'}$ ,  $R^{2b'}$ ,  $R^3$ ,  $R^{4a}$ ,  $R^{4b}$ ,  $R^5$ ,  $R^{13}$ ,  $R^{14}$ , D, E, V and Z have the meanings already mentioned, and  $PG^{14}$  represents a hydrogen atom or a protective group PG, and this partial fragment AB is reacted with a fragment of

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general formula C



C

in which

- $R^8$  has the meaning already mentioned in general formula I for  $R^8$ , and
- $R^7$  means a hydrogen atom,
- $R^{20}$  means a hydrogen atom or a protective group  $PG^2$ ,
- $R^{21}$  means a hydroxy group, halogen, a protected hydroxy group  $OPG^3$ , a phosphonium halide radical  $PPh_3^+Hal^-$  (Ph = phenyl; Hal = F, Cl, Br, I), a phosphonate radical  $P(O)(OQ)_2$  ( $Q = C_1-C_{10}$  alkyl or phenyl) or a phosphine oxide radical  $P(O)Ph_2$  (Ph = phenyl),
- U means an oxygen atom, two alkoxy groups  $OR^{23}$ , a  $C_2-C_{10}$  alkylene- $\alpha,\omega$ -dioxy group, which can be straight-chain or branched,  $H/OR^9$  or a grouping  $CR^{10}R^{11}$ ,
- whereby
- $R^{23}$  stands for a  $C_1-C_{20}$  alkyl radical,
- $R^9$  stands for hydrogen or a protective group  $PG^3$ ,
- $R^{10}$ ,  $R^{11}$  are the same or different and stand for hydrogen, a  $C_1-C_{20}$  alkyl, aryl,  $C_7-C_{20}$  aralkyl radical or  $R^{10}$  and  $R^{11}$  together with the methylene

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Sub  
BI  
cont.



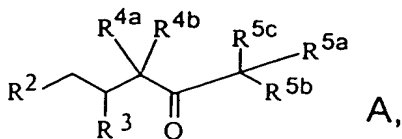
10. Pharmaceutical preparations that contain at least one compound of general formula I according to claim 1, as well as a pharmaceutically compatible vehicle.

12. Process for the production of compounds of general

12. Process for the production of compounds of general



formula A



in which

*Sub B' com.*  
 R<sup>2</sup> means CH<sub>2</sub>OR<sup>2a</sup>, CHO, CO<sub>2</sub>R<sup>2b</sup>, COX,

R<sup>2a</sup>, R<sup>2b</sup> mean hydrogen, C<sub>1</sub>-C<sub>20</sub> alkyl, aryl, C<sub>7</sub>-C<sub>20</sub> aralkyl,

R<sup>3</sup> means hydrogen, OR<sup>3a</sup>, X, OSO<sub>2</sub>R<sup>3b</sup>,

R<sup>3a</sup> means hydrogen or together with R<sup>2a</sup> a -(CH<sub>2</sub>)<sub>n</sub> group or a CR<sup>6a</sup>R<sup>6b</sup> group,

R<sup>3b</sup> means C<sub>1</sub>-C<sub>4</sub> alkyl, aryl,

X means halogen,

n means 2 to 4,

R<sup>6a</sup>, R<sup>6b</sup> are the same or different and mean C<sub>1</sub>-C<sub>8</sub> alkyl, C<sub>6</sub>-C<sub>10</sub> aryl or together a -(CH<sub>2</sub>)<sub>o</sub> group,

o means 3 to 6,

R<sup>6a</sup> additionally can assume the meaning of hydrogen,

R<sup>4a</sup>, R<sup>4b</sup> are the same or different and mean hydrogen, C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>7</sub>-C<sub>20</sub> aralkyl or together a -(CH<sub>2</sub>)<sub>m</sub> group,

m means 2 to 5,

R<sup>5a</sup>, R<sup>5b</sup> are the same or different and mean hydrogen, C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>7</sub>-C<sub>20</sub> aralkyl or together a -(CH<sub>2</sub>)<sub>p</sub> group,

p means 2 to 5,

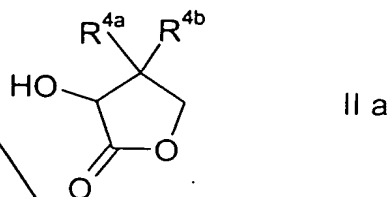
R<sup>5c</sup> means hydrogen,

including all stereoisomers and mixtures thereof,

and

free hydroxyl groups can be etherified or esterified in  $R^2$  and  $R^3$ , free carbonyl groups can be ketalized in A and  $R^2$ , converted into an enol ether or reduced, and free acid groups in A can be converted into their salts with bases, wherein

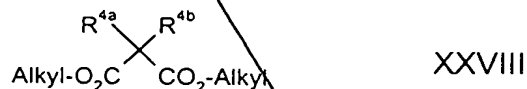
a) a pantolactone of general formula IIa or



in which

$R^{4a}$  and  $R^{4b}$  in each case are methyl groups or

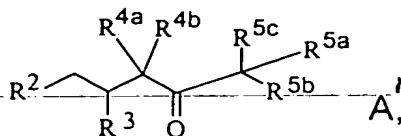
b) a malonic acid dialkyl ester of general formula XXVIII



in which

$R^{4a}$ ,  $R^{4b}$ , which have the meaning that is indicated in general formula A, and alkyl, independently of one another, mean a  $C_1$ - $C_{20}$  alkyl,  $C_3$ - $C_{10}$  cycloalkyl or  $C_4$ - $C_{20}$  alkylcycloalkyl radical, is used as a starting product.

13. Compounds of general formula A'



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in which

$R^2$  means  $CH_2OR^{2a}$ ,  $CHO$ ,  $CO_2R^{2b}$ ,  $COX$ ,

$R^{2a}$ ,  $R^{2b}$  mean hydrogen,  $C_1-C_{20}$  alkyl, aryl,  $C_7-C_{20}$  aralkyl,

$R^3$  means hydrogen,  $OR^{3a}$ ,  $X$ ,  $OSO_2R^{3b}$ ,

$R^{3a}$  means hydrogen or together with  $R^{2a}$  a  $-(CH_2)_n$  group or a  $CR^{6a}R^{6b}$  group,

$R^{3b}$  means  $C_1-C_4$  alkyl, aryl,

$X$  means halogen,

$n$  means 2 to 4,

$R^{6a}$ ,  $R^{6b}$  are the same or different and mean  $C_1-C_8$  alkyl,  $C_6-C_{10}$  aryl or together a  $-(CH_2)_o$  group,

$o$  means 3 to 6,

$R^{6a}$  additionally can assume the meaning of hydrogen,

$R^{4a}$ ,  $R^{4b}$  are the same or different and mean hydrogen,  $C_1-C_{10}$  alkyl,  $C_7-C_{20}$  aralkyl or together a  $-(CH_2)_m$  group,

$m$  means 2 to 5,

$R^{5a}$ ,  $R^{5b}$  are the same or different and mean hydrogen,  $C_1-C_{10}$  alkyl,  $C_7-C_{20}$  aralkyl or together a  $-(CH_2)_p$  group,

$p$  means 2 to 5,

$R^{5c}$  means hydrogen,

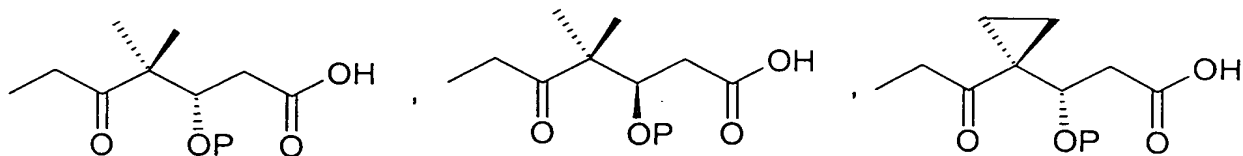
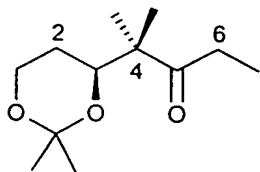
including all stereoisomers and mixtures thereof,

and

free hydroxyl groups can be etherified or esterified in  $R^2$  and  $R^3$ , free carbonyl groups can be ketalized in A and  $R^2$ , converted into an enol ether or reduced, and free acid groups in A can be converted into their salts with bases,

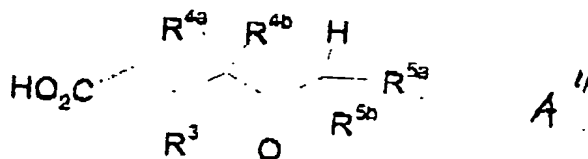
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excluding the compounds



P = TBS

14. Process for the production of compounds of general formula A''



in which

$R^3$  means  $OR^{3a}$  and

$R^{3a}$  means hydrogen or a protective group PG

$R^{4a}$ ,  $R^{4b}$  are the same or different and mean hydrogen,

$C_1$ - $C_{10}$ -alkyl,  $C_7$ - $C_{20}$ -aralkyl, or together a  $-(CH_2)_m$  group,

m means 2-5,

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$R^{5a}$ ,  $R^{5b}$  are the same or different and mean hydrogen,  
 $C_1-C_{10}$ -alkyl,  $C_7-C_{20}$ -aralkyl, or together a  $-(CH_2)_p$   
 group,

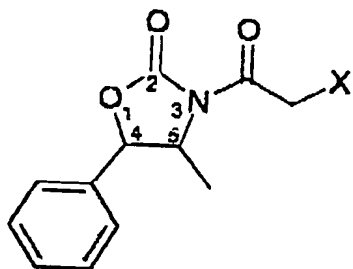
$p$  means 2-5,

including all stereoisomers and mixtures thereof,

and

free carbonyl groups can be ketalized in A",

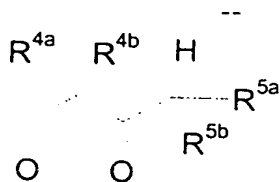
wherein a compound of general formula II



II

in which

$X$  is a chlorine or bromine atom, and the 2-oxazolidinone  
 ring has either a (4R,5S) or a (4S,5R) conformation,  
 is reacted with a compound of general formula III



III

in which

$R^{4a}$ ,  $R^{4b}$  are the same or different and mean hydrogen,

$C_1-C_{10}$ -alkyl,  $C_7-C_{20}$ -aralkyl, or together a  $-(CH_2)_m$  group,

$m$  means 2-5,

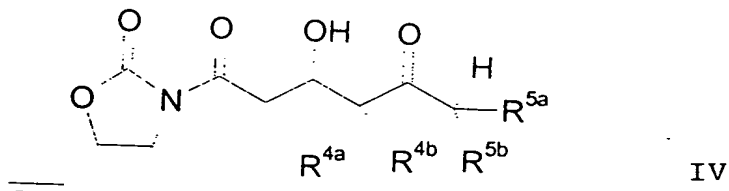
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$R^{5a}$ ,  $R^{5b}$  are the same or different and mean hydrogen,

$C_1$ - $C_{10}$ -alkyl,  $C_7$ - $C_{20}$ -aralkyl, or together a  $-(CH_2)_p$  group,

p means 2-5,

to a compound of general formula IV



in which

the 2-oxazolidinone ring (4R,5S) and the 3'-carbon atom have an R conformation, or

the 2-oxazolidinone ring (4S,5R) and the 3'-carbon atom have an S conformation,

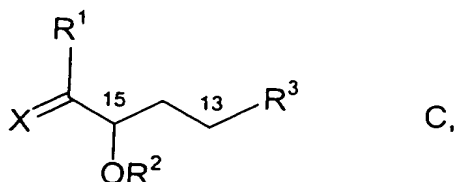
the 3'-hydroxy group in IV is protected by a protective group PG, the oxazolidinone ring is cleaved, and protective group PG is optionally cleaved.

15. Process according to claim 14, wherein the compound of general formula II is reacted in the presence of chromium(II) chloride with a compound of general formula III.

16. Process according to claim 14 or 15, wherein the cleaved oxazolidinone ring is recovered in an enantiomer-pure manner.

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~~17~~ Compounds of general formula C



in which

$\text{R}^1$  means hydrogen,  $\text{C}_1\text{-C}_{20}$  alkyl, aryl,  $\text{C}_7\text{-C}_{20}$  aralkyl, which can all be substituted,

$\text{R}^2$  means hydrogen or a protective group  $\text{PG}^1$ ,

$\text{R}^3$  means a hydroxy group, halogen, a protected hydroxy group  $\text{OPG}^2$ , a phosphonium halide radical  $\text{PPh}_3^+\text{Hal}^-$  (Ph = phenyl; Hal = F, Cl, Br, I), a phosphonate radical  $\text{P}(\text{O})(\text{OQ})_2$  ( $\text{Q} = \text{C}_1\text{-C}_{10}$  alkyl or phenyl) or a phosphine oxide radical  $\text{P}(\text{O})\text{Ph}_2$  (Ph = phenyl),

X means an oxygen atom, two alkoxy groups  $\text{OR}^4$ , a  $\text{C}_2\text{-C}_{10}$  alkylene- $\alpha,\omega$ -dioxy group, which can be straight-chain or branched,  $\text{H/OR}^5$  or a grouping  $\text{CR}^6\text{R}^7$ ,  
whereby

$\text{R}^4$  stands for a  $\text{C}_1\text{-C}_{20}$  alkyl radical,

$\text{R}^5$  stands for hydrogen or a protective group  $\text{PG}^3$ ,

$\text{R}^6, \text{R}^7$  are the same or different and stand for

hydrogen, a  $\text{C}_1\text{-C}_{20}$  alkyl, aryl,  $\text{C}_7\text{-C}_{20}$  aralkyl radical or  $\text{R}^6$  and  $\text{R}^7$  together with the methylene carbon atom together stand for a 5- to 7-membered carbocyclic ring,

whereby not simultaneously

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21. Compounds of general formula C according to claim 20,  
wherein the aryl radical that stands for R<sup>6</sup> and/or R<sup>7</sup> is selected  
from the group 2-, 3-furanyl; 2-, 3-, 4-pyridinyl; 2-, 4-, 5-



thiazolyl; 2-, 4- and 5-imidazolyl radical, which optionally is substituted by 1 or 2 C<sub>1</sub>-C<sub>4</sub> alkyl radicals.

22. Compounds of general formula C according to claim 17, wherein protective groups PG<sup>1</sup>, PG<sup>2</sup>, and PG<sup>3</sup> are selected from the group of substituents methoxymethyl, methoxyethyl, ethoxyethyl, tetrahydropyranyl, tetrahydrofuranyl, trimethylsilyl, triethylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, tribenzylsilyl, triisopropylsilyl, benzyl, para-nitrobenzyl, para-methoxybenzyl, formyl, acetyl, propionyl, isopropionyl, pivalyl, butyryl, or benzoyl radical.

23. Compounds according to claim 18, wherein protective group PG<sup>4</sup> is selected from the group of substituents methoxymethyl, methoxyethyl, ethoxyethyl, tetrahydropyranyl, tetrahydrofuranyl, trimethylsilyl, triethylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, tribenzylsilyl, triisopropylsilyl, benzyl, para-nitrobenzyl, para-methoxybenzyl, formyl, acetyl, propionyl, isopropionyl, pivalyl, butyryl or benzoyl radical.

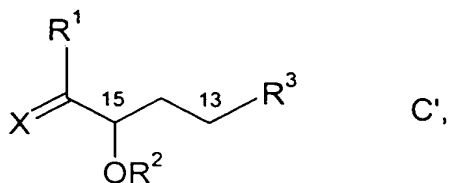
24. Compounds according to claim 20, wherein protective group PG<sup>5</sup> is selected from the group of substituents methoxymethyl, methoxyethyl, ethoxyethyl, tetrahydropyranyl, tetrahydrofuranyl, trimethylsilyl, triethylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, tribenzylsilyl, triisopropylsilyl, benzyl, para-nitrobenzyl, para-methoxybenzyl, formyl, acetyl, propionyl, isopropionyl, pivalyl, butyryl or benzoyl radical.

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25. Compounds according to claim 22, wherein protective group PG<sup>1</sup> is a tert-butyldiphenylsilyl, tert-butyldimethylsilyl or triisopropylsilyl radical.

26. Compounds according to claim 22, wherein protective group PG<sup>2</sup> is a tert-butyldimethylsilyl, acetyl, benzoyl, benzyl or tetrahydropyranyl radical.

27. Process for the production of compounds of general formula C'



in which

R<sup>1</sup> means hydrogen, C<sub>1</sub>-C<sub>20</sub> alkyl, aryl, C<sub>7</sub>-C<sub>20</sub> aralkyl, which can all be substituted,

R<sup>2</sup> means hydrogen or a protective group PG<sup>1</sup>,

R<sup>3</sup> means a hydroxy group, halogen, a protected hydroxy group OPG<sup>2</sup>, a phosphonium halide radical PPh<sub>3</sub><sup>+</sup>Hal<sup>-</sup> (Ph = phenyl; Hal = F, Cl, Br, I), a phosphonate radical P(O)(OQ)<sub>2</sub> (Q=C<sub>1</sub>-C<sub>10</sub> alkyl or phenyl) or a phosphine oxide radical P(O)Ph<sub>2</sub> (Ph = phenyl),

X means an oxygen atom, two alkoxy groups OR<sup>4</sup>, a C<sub>2</sub>-C<sub>10</sub> alkylene-α,ω-dioxy group, which can be straight-chain or branched, H/OR<sup>5</sup> or a grouping CR<sup>6</sup>R<sup>7</sup>,

whereby

R<sup>4</sup> stands for a C<sub>1</sub>-C<sub>20</sub> alkyl radical,

R<sup>5</sup> stands for hydrogen or a protective group PG<sup>3</sup>,

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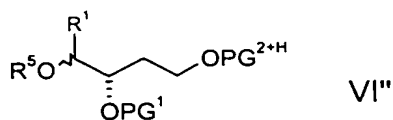
$R^6, R^7$  are the same or different and stand for

hydrogen, a  $C_1-C_{20}$  alkyl, aryl,  $C_7-C_{20}$  aralkyl radical or  $R^6$  and  $R^7$  together with the methylene carbon atom together stand for a 5- to 7-membered carbocyclic ring,

wherein L-(-)-malic acid, D-(+)-malic acid or racemic malic acid is used as a starting product.

28. Process according to claim 27, wherein L-(-)-malic acid or D-(+)-malic acid is used.

29. Intermediate compounds of general formula VI"



in which

$R^1, PG^1$  and  $R^5$  have the meaning that is indicated in general formula C, and

$PG^{2+H}$  stands for a hydrogen atom or a protective group  $PG^2$ .

30. Process for the production of the compounds of general formula VI" according to claim 29, wherein an organometal compound of general formula



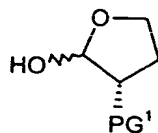
in which

$R^1$  has the meaning that is indicated in general formula C', and

Y stands for an alkali metal atom or MZ, whereby M is a divalent metal atom and Z is a halogen atom,

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is added to a compound of general Formula IV

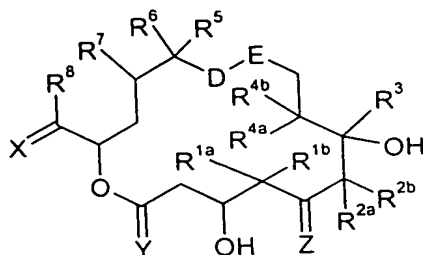


in which

PG<sup>1</sup> has the meaning that is indicated in general Formula C, while the lactol ring is opened, and then optionally the primary hydroxy group is protected with a protective group PG<sup>2</sup> and optionally the secondary group is protected with a protective group PG<sup>3</sup>.

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This invention relates to the new epothilone derivatives of general formula I,



1.

substituents Y, Z, R<sup>2a</sup>, R<sup>2b</sup>, R<sup>3</sup>, R<sup>4a</sup>, R<sup>4b</sup>, D-E, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup> and X have the meanings that are indicated in more detail in the description.

The new compounds interact with tubulin by stabilizing microtubuli that are formed. They are able to influence the cell-splitting in a phase-specific manner and are suitable for treating malignant tumors, for example, ovarian, stomach, colon, adeno-, breast, lung, head and neck carcinomas, malignant melanomas, acute lymphocytic and myelocytic leukemia. In addition, they are suitable for anti-angiogenesis therapy as well as for treatment of chronic inflammatory diseases (psoriasis, arthritis). To avoid uncontrolled proliferation of cells and for better compatibility of medical implants, they can be applied or introduced into polymer materials.

The compounds according to the invention can be used alone or to achieve additive or synergistic actions in combination with

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other principles and classes of substances that can be used in tumor therapy.

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